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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,953	02/13/2001	R. Sanders Williams	UTSD:674US/SLH	2337

7590 04/20/2005

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,953	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Samuel W. Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59,61,62 and 70* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59,61,62 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 59, 61-62 and 70 are pending.

Applicants' amendment filed 1/31/05 which amends claim 59 has been entered. Also, the applicants' request for extension of time of two months has been entered. The following Office action is applied to the pending claims 59, 61-62 and 70.

Please note that the objection(s) and/or rejection(s) not explicitly stated and/or restated below are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 59, 61-62 and 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 recites "modulating muscle cell growth"; the recitation is not clear as to whether or not the modulation refers to increasing or decreasing muscle cell growth. See also the claim item *a*), "muscle cell growth modulation". Also, claim 59 is indefinites in "a small molecule modulator" because specification provides insufficient definition for it; does it refer to any molecules ranging from inorganic molecules to organic compounds including small nucleotide/nucleoside or nucleic acid molecule as well as small nuclear ribonucleoproteins? The dependent claims (61, 62 and 70) are also rejected.

Claim 61 recited that "small molecule modulator is an *agonist*" while claim 62 recites that "small molecule modulator is an *antagonist*". These recitations are not apparent because the claim does not make it clear as to whether or not the agonist or antagonist acts on same subject or separate subject; given the same subject, how can the small molecule modulator function as both agonist and antagonist simultaneously?

Claim 70 recites "a second pharmaceutical agent"; the recitation is unclear regarding whether or not the said pharmaceutical agent comprises the modulator of claim 59. Does said second pharmaceutical agent differ from the first pharmaceutical agent? Additionally, claim 70 is unclear as to whether or not said second pharmaceutical agent is co-administered with the first pharmaceutical agent. Is the second pharmaceutical agent same as the small molecule modulator (claim 59)?

The applicants' response to the rejection under 35 USC112, second paragraph

The response filed 1/31/05 argues that the language "modulating" is not indefinite as, by definition, modulation refers to alteration in any direction up or down according to modulating MCIP expression (see pages 4-5). The applicants' argument is found to be unpersuasive because without making it clear as to which process/mechanism, i.e., up- or down-modulation, the current invention refers, the claim is considered to be indefinite and because of the reason set forth above.

Also, the response asserts that claims 61 and 62 are clear as they set forth the limitations individually ("agonist" and "antagonist", respectively) onto claim 59 from which they depend, and the "*agonist*" and "*antagonist*" relate to up-modulation and down-modulation, respectively

(see page 5, the 2d paragraph). The applicants' argument is found to be unpersuasive because of the reason stated above, and because, given a target subject, the claimed modulator (claim 59) cannot simultaneously act as both full agonist and full antagonist to regulate the muscle cell growth.

Further, the response discusses the issue with regard to the recitation "second pharmaceutical agent" (page 5, the 3rd paragraph), and asserts that the recitation is relative to the agent (the first one) recited in claim 59. The applicants' argument has been considered but is unpersuasive because there is insufficient antecedent basis for "second pharmaceutical agent " in claim 59 from which claim 70 depends, and because claim 70 per se does not make it clear as to what is relation between said second pharmaceutical agent and the agent set forth in claim 59.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C.

122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The claims 59, 62 and 70 are rejected under 35 U.S.C. 102(e) as being anticipated by Edge, A. (US Pat. No. 6673604) as is evidenced by the known fact disclosed in the reference Sussman M. A. et al. (*Science* (1998) 281, 1690-1693) which teaches that cyclosporin is an inhibitor of the calcineurin stimulation of muscle growth.

In Example 1, Edge teaches a method of regulating growth of a striated muscle, i.e., myocardial muscle, in a human subject comprising choosing human myocardial cells as the subject, selecting and administering cyclosporine to the subject wherein cyclosporin is an inhibitor (antagonist, *claim 62*) of the calcineurin which has ability of stimulating the muscle cell growth as evidenced by the Sussman' reference (see page 1690).

Note that, when administered to the subject, the cyclosporin would unavoidably down-regulate the muscle growth regardless of that in which process, e.g., cellular therapy for myocardial repair as set forth in the Edge's Example 1 the administration is carried out, and note that striated muscle cells encompasses cardiac muscle cells.

Thus, the above Edge's teaching anticipates the instant claims 59 and 62.

Also, in Example 1, Edge teaches that, in addition to the cyclosporin, a pharmaceutical agent, i.e., prednisone, is administered to the subject, which anticipated the instant claim 70.

*Please note that the above rejection is applicable due to the fact that Applicant's amendment necessitated this new ground of rejection (see the amended claim 1 where recites "**striated** muscle cell growth modulation".*

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 59, 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chin, E. R. et al. (*Gene Dev.* (1998) 12, 2499-2509).

Chin et al. teach a process of modulating skeletal and cardiac muscle (i.e., striated muscle) cell growth comprising selecting a mammal (rat) subject, selecting a small molecule (i.e., cyclosporin that is a specific inhibitor for calcineurin (see page 2502, the right column, lines 10-14) for calcineurin which is an active regulator for muscle cell growth, and administering the cyclosporin A to the subject (see abstract and pages 2502-2503, the section "*administration of the calcineurin antagonist cyclosporin A to intact animal promotes slow-to-fast fiber transformation*"). The Chin et al. teaching is applied to the instant claim 59.

In Figures 4-5, Chin et al. show that cyclosporin A has reciprocal effects on muscle cell growth through reducing slow myosin expression and enhancing fast myosin expression (see also the left column at page 2503 and page 2506), which is applied to the instant claims 61 and 62.

Please note that the current invention is directed to a method of modulating muscle cell growth by administering to a subject a modulator but NOT to a method of modulating MCIP1 expression, and that the modulator-mediated regulation of MCIP1 is regarded as a mechanistic step. Thus, the above Chin et al. teachings are applicable to the above-mentioned claims.

Chin et al. do not explicitly teach that the subject of above motioned process of modulating muscle cell is a *human* subject.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to readily applied the Chin's method to the human subject because Chin et al. reference has suggested that the therapeutic agent (e.g., cyclosporin A) capable of modifying calcineurin activity selectively in skeletal muscles can be used in human subjects (see the left column, lines 1-3 at page 2507). Also, Chin et al. teach that a signaling pathway involved in mammalian skeletal muscle growth is cyclosporin-sensitive (see abstract). Thus, the skilled artisan would have applied the Chin's method to regulate muscle cell growth in a human subject and would have successfully arrived at the current invention. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Claims 59, 62 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sussman M. A. et al. (*Science* (1998) 281, 1690-1693).

Sussman et al. teach a process of modulating cardiac muscle (*note that cardiac muscle belongs to striated muscle*) cell growth comprising providing a small molecule inhibitor for calcineurin, i.e., cyclosporin, and administering the cyclosporin to a subject, e.g., transgenic mice (see abstract, Figures 1-2, and pages 1690-1691 and 1693), wherein calcineurin is an activator for induction of MCIP1 (myocyte-enriched calcineurin-interacting protein) expression, and cyclosporin is an inhibitor (i.e., antagonist) of the calcineurin for muscle growth (see page 1690, the right column, the last paragraph). Note that calcineurin is an active regulator for muscle cell growth. Thus, the Sussman et al. teachings are applied to claims 59 and 62 of the current application.

Further, Sussman et al. teach administration of cyclosporin and FK506 (the second pharmaceutical agent) (see abstract), which is applied to claim 70 of the current application.

Sussman et al. do not explicitly teach that the subject is a human subject (the reference teaches use of transgenic mice as a model for investigation).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to readily applied the Sussman's method to the human subject. One skilled in the art would have been motivated to do this because Sussman et al. reference has suggested that cyclosporin treatment of muscle growth-related hypertrophy (see Figure 1) is applied to human subject (see abstract, the last sentence), and also suggested that the said treatment is of potential therapeutic for certain forms of human heart disease (see abstract). Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

The applicants' response to the rejection under 35 USC 103(a)

On pages 7-8, the response filed 1/31/05 argues that the Chin et al. and Sussman et al. references improperly rely on inherency (i.e., modulating MCIP is performed through regulating calcineurin), and that the inherency is not necessarily known, and thus, obviousness cannot be predicted on what is unknown (page 7, the 2nd paragraph). Also, the response asserts that Chin's and Sussman's references existed before the knowledge of MCIP's role in muscle biology; and thus, applicants infers that the fact that calcineurin regulates MCIP (expression) does not make it obvious to the skilled artisan that modulation of MCIP is accomplished by modulating calcineurin. The applicants' argument is found to be not persuasive because when administration of cyclosporine to the subject inevitably leads to regulating (up- or down-) the muscle cell growth, and because the claimed method is directed to regulating muscle cell growth but not the MCIP's expression itself which is considered to be a molecular mechanistic step of the regulation. Therefore, it is not required for one skilled in the art to know the mechanism thereof before the skilled artisan carries out the claimed method, i.e., regulating muscle cell growth comprising administering to the subject the small molecule modulator – cyclosporin and successfully arrive at the claimed invention. Thus, the above-mentioned inherency is not a determinant here for qualification of the Chin's and Sussman's references as prior art for obviousness.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A

shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Weber, Jon, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel W. Liu, Ph.D.

April 5, 2005

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER